Remarks

Claims 1-63 are pending in this application. The Examiner withdrew claims 10, 11, 14, 15, 26-30, and 33-39 in response to a restriction requirement. The Applicants have added claims 41-63. Support for new claims 41-43 may be found in claims 3 and 4 as originally filed; support for new claims 44-63 may be found at ¶ 0203 of the specification. The Applicants have not added any new matter.

The Examiner objected that the specification recites two sequences without assigning them a sequence identification number. The Applicants have amended the specification to assign these sequences the identifiers SEQ ID NO: 39 and SEQ ID NO: 40, respectively. The specification recites these sequences at ¶¶ 0595 and 0598. The Applicants have amended the sequence listing by adding these sequences, and submit with this Amendment.

The Examiner objected that the specification recites "SEQ ID Nº 1-4," whereas it should recite "SEQ ID NOS: 1-4," instead. The Applicants have amended the specification to correct this typographical error.

The Applicants note the Examiner's admonition regarding the use of trademarks. The Applicants have corrected ¶ 0549 of the specification to recite "verapamil" in the lower case, without the "tm" symbol, as that term is not a trademark. The Applicants have amended ¶ 0560 to add a trademark symbol (™) to the term "SuperScript," and have rendered it in the same manner as the trademark owner (i.e., capitalizing both "S"s). Finally, the Applicants have amended ¶ 0564 to recite "ABI Prism" with a symbol (®) showing that the term is a registered mark.

The Examiner objected to claims 16 and 17 under 37 C.F.R. § 1.75(c), stating that, as a multiple dependant claims, claims 16 and 17 cannot depend from any other multiple claim. The Examiner further objected to claim 16, pointing out that the Markush format of the claim requires an "and" between the last two species. The Applicants have amended claims 16 and 17 by placing them into proper format. The Applicants respectfully request that the Examiner withdraw the rejection under § 1.75(c).

The Examiner rejected claims 21, 22, 24, and 25, under 35 U.S.C. § 101, stating that they read on cloned humans. The Examiner suggested that amending the claims to recite "an isolated host cell," instead of "a host cell," would obviate this rejection. The Applicants have done as the Examiner suggested, adding the term "isolated" to claims 21, 24, and 25. Support for the term is found at ¶ 0169. The Applicants respectfully request that the Examiner withdraw the objection under

§ 101.

The Examiner further rejected claims 1-9, 12, 13, 16-25, 31-32, and 40 under 35 U.S.C. §§ 101 and 112, first paragraph, stating that the claims are not supported by a specific and substantial asserted utility or a well established utility. The Examiner stated that the Applicants "have not stated that any diseases are known to be associated with ABCA12 proteins, and Applicants have not provided an activity for ABCA12 proteins." The Applicants respectfully disagree.

The Applicants teach that the ABCA12 protein is associated with pathologies linked to the 2q34 locus of human chromosome 2, particularly the skin disorder lamellar ichthyosis:

> we [the Applicants] have mapped the novel ABCA12 gene in a region located in the 2q34 locus of human chromosome 2, which is statistically linked with lamellar ichtyosis, polymorphic congenital cataract, and insulin dependant diabete[s] mellitus.

Specification, at ¶ 0025 (citations omitted); see also ¶ 0027 (reiterating that ABCA12 is involved in pathologies associated with the 2q34 locus of chromosome 2) and Fig. 1. Hence, the invention in one of its embodiments relates to a method of treating a patient with a disorder, such as lamellar ichthyosis, associated with the 2q34 locus of human chromosome 2. *See, e.g., Id.,* at ¶ 0093 (disclosing that the invention "relates to a treatment of a patient or a subject affected by a pathology located on the chromosome locus 2q34, such as . . . the ichthyosis lamellar"), ¶¶ 0095-0097, 0099-0103, 0131, 0133, 0138-0140, 0142, 0143-144 (providing examples of methods to treat patients with a pathology located on locus 2q34, such as lamellar Ichtyosis), and original claim 34.

Lamellar ichtyosis is a inherited autosomal recessive disorder of cornification, and is accompanied by keratoderma, alopecia and erythema. Specification, at ¶ 0022. The contention that ABCA12 is associated with this skin disorder is bolstered by the Applicants' data suggesting that ABCA12 is distributed preferably in the skin:

> an electronic analysis of tissue distribution has been performed, and sequence of the ABCA12 transcript has been shown to match with various ESTs generated by skin/epithelial cell cDNA library sequencing, suggesting a preferential tissue expression in the skin/epithelium.

At ¶ 0026.

Still additional data, reported by C. Lefèvre *et al.*, Hum. Molec. Gen., 12: 2369-2378 (2003) and enclosed herewith, support the contention that ABCA12 is associated with lamellar ichtyosis. The authors analyzed 56 subjects (15 patients with lamellar ichthyosis, 41 healthy) in nine families and, after excluding other potential gene candidates, traced the disease to five missense mutations in four exons of the ABCA12 gene. *See* the first paragraph at 2370, above "Results," and the third paragraph, under "Linkage, linkage disequilibrium and haplotype analysis." In the course of sequencing candidate genes, moreover, the authors obtained a sequence that corresponds to the Applicants' ABCA12. *See* the first paragraph at 2372 ("This mRNA sequence corresponds to the recently described patent sequence I (AX587156). . . .).

In sum, the application recites an association between the claimed ABCA12 gene and an important skin disorder, and recent data only confirm the association. The Applicants respectfully submit, therefore, that the claims define an invention with a substantial, credible, and specific utility, and respectfully request that the Examiner withdraw the rejection under §§ 101 and 112, first paragraph.

The Examiner rejected claims 2-5 under §112, first paragraph, stating that the specification neither enables or describes polynucleotides that are 80%-98% identical to SEQ ID NOS: 1, 2, 3, or 4, polynucleotides that hybridize with a nucleotide sequence comprising at least 8 consecutive nucleotides of SEQ ID NOS: 1, 2, 3, or 4, or polynucleotides that hybridize with a nucleotide sequence comprising SEQ ID NOS: 1, 2, 3, or 4. The Applicants respectfully disagree.

The specification speaks at length about methods to produce ABCA12 derivatives, at both the gene and protein level, resulting in sequences that are at least 80-98% identical to the sequences of SEQ ID NOS: 1, 2, 3, and 4. *See generally* ¶¶ 0253-0262. The specification defines various amino acid substitutions at ¶ 0254 (e.g., substituting non-polar amino acids such as alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine with another non-polar amino acid; substituting a positively charged amino acid such as arginine, lysine, and histidine with another positively charged amino acid; etc.), and particularly preferred substitutions at ¶¶ 0255-0260 (e.g., Lys for Arg and Glu for Asp), and describes various mutation techniques for modifying the nucleic acid sequence. Moreover, many of these techniques are well known in the art, as the specification points out.

In addition, the specification does more than provide a single example of ABCA12: it recites four, two with different polyadenlyation sites, and two splicing

forms. *See, e.g,* ¶ 0024. In view of the foregoing, the Applicants respectfully submit that preparing a nucleic acid comprising a sequence having at least 80-98% identity with SEQ ID NOS: 1, 2, 3, or 4, or that hybridizes to those sequences, would be readily apparent to one of ordinary skill in the art. The Applicants note, moreover, that the level of skill in the art of microbiology is quite high, and the techniques employed (and described, for example, at ¶¶ 0255-0260) are well known in the art. The Applicants therefore respectfully request that the Examiner withdraw the rejection under § 112 with respect to claims 2-5.

The Examiner rejected claims 1-8, 13, 16-21 and 31 under § 112, second paragraph, stating that the Applicants' use of the term "complementary" is unclear. The Applicants have amended the claims to clarify this term, and respectfully request that the Examiner remove the rejection under § 112, second paragraph, with respect to these claims.

The Examiner rejected claim 5 under § 112, second paragraph, stating that the term "high stringent conditions" is indefinite. The Applicants have amended that claim to recite precise hybridization conditions, and respectfully submit that the claim comports fully with § 112, second paragraph. The Applicants respectfully request, therefore, that the Examiner withdraw the rejection of claim 5 under § 112, second paragraph.

The Examiner rejected claims 2, 5, 7, and 16 under 35 U.S.C. § 102(b) as being anticipated by the sequence of GenBank Acc. No. AQ743553 (Mahairas *et al.*). The Examiner stated that that sequence is identical to the SEQ ID NOS: 1-4 over a span of 153 bases. The Applicants have amended claims 2, 5, 7 and 16 such that they are now directed to sequences at least 154 nucleotides long, and have added new dependent claims 44-63 to further define the minimum length. The Applicants respectfully submit that the sequence of Mahairas *et al.* does not disclose or suggest a sequence of that length that has the limitations that claims 2, 5, 7, and 16 require, and respectfully request, therefore, that the Examiner withdraw the rejection as to those claims under § 102(a).

The Applicants respectfully submit that the claims, as amended, are in condition for allowance, and respectfully request early, favorable action on the application. Should the Examiner believe that an interview would advance the prosecution of this application, the Applicants invite her to contact the undersigned at 908.231.3444.

Respectfully submitted,

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